P-selectin mediates the interaction of circulating leukocytes with platelets and microvascular endothelium in response to oxidized lipoprotein in vivo.

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BACKGROUND: Oxidized low density lipoprotein (oxLDL) has been demonstrated to stimulate leukocyte/endothelium interaction, an early feature of atherogenesis. Using the skinfold chamber model for intravital microscopy in hamsters and mice, we have shown that oxLDL-induced leukocyte adhesion to microvascular endothelium shares many characteristics with leukocyte adhesion during inflammation and ischemia/reperfusion, including the involvement of beta 2 integrin adhesion molecules. In light of the two-step model of leukocyte adhesion, we have examined the contribution of P-selectin to oxLDL-induced leukocyte/endothelium interaction. P-selectin is an inducible adhesion molecule on platelets and endothelium, mediating the initial steps of leukocyte margination and rolling along the endothelial lining, as well as of aggregate formation between platelets and leukocytes. EXPERIMENTAL DESIGN: For our studies, we used the dorsal skinfold chamber model for intravital fluorescence microscopy on awake Syrian golden hamsters. Hamsters were treated 10 minutes before oxLDL-injection (oxidized by Cu2+, 4 mg/kg body weight, intravenously) with blocking antibodies to P-selectin (2 mg/kg body weight intravenously, N = 7). RESULTS: In seven control animals (pretreated with an irrelevant IgG antibody), oxLDL injection elicited leukocyte rolling and adhesion on both venular and arteriolar endothelium, and also the formation of aggregates tumbling down the microvessels and firmly adhering to the microvascular endothelium. The aggregates consisted of leukocytes and **activated , dendritic platelets** , as assessed by scanning electron microscopy of the buffy coat isolated by density gradient centrifugation of whole blood taken from hamsters 15 minutes after injection of oxLDL. Leukocyte adhesion to venular and arteriolar endothelium, as well as the formation of leukocyte/platelet aggregates were significantly reduced by pretreatment of the animals with anti-P-selectin antibodies. CONCLUSIONS: These data emphasize the similarities between leukocyte adhesion in response to oxLDL and in other pathophysiologic conditions, identifying P-selectin as a crucial player in the interaction between leukocytes and microvascular endothelium as well as in the formation of circulating leukocyte/platelet aggregates.

Title: Anti-phospholipid antibodies opsonize activated platelets **for uptake by** dendritic **cells: relevance to epitope spreading in platelet autoimmunity.**

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S1	139	(ACTIVAT? (2N) PLATELET?) (S) DENDRITIC
S2	71	S1 NOT PY>1999
S3	32	RD (unique items)
S4	68	(ACTIVATED (2N) PLATELET?) (S) (DENDRITIC OR DCS)
S5	37	S4 NOT PY>1998
S6	16	RD (unique items)

S7	135	(E(W)L) (2N) SELECTIN?
S8	84	S7 NOT PY>1999
S9	71	S8 NOT PY>1998
S10	13	S8 NOT S9
S11	4	RD (unique items)
S12	8	S9 AND (CHIMER? OR FUSED OR FUSION)
S13	2	RD (unique items)
S14	21357	E/L (W)SELECTIN?
S15	31	(E(W)L)(W)SELECTIN?
S16	15	RD (unique items)